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| EXAMINER |
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MOORE, WILLIAM W

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| ART UNIT | PAPER NUMBER |
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1656

DATE MAILED: 05/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/743,647

Applicant(s)

PANGALOS ET AL.

Examiner

William W. Moore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 February 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-48 is/are pending in the application.
- 4a) Of the above claim(s) 1-9 and 12-48 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10 and 11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: See Continuation Sheet.

Continuation of Attachment(s) 6). Other: Notice to Comply with 37 CFR 1.821.

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DETAILED ACTION

Priority

Applicant's claim in the Declaration of Inventorship to priority under 35 U.S.C. §§ 119 and 371 of the 14 July 1998 filing date of British patent application No. 9815284.6, and its successor International patent application PCT/GB99/02241 filed 14 July 1999, is hereby acknowledged. The claim to priority with regard to the elected NAALADase-L protease is accorded to British patent application No. 9815284.6 filed 14 July 1998 in view of the fact that this publication is the first disclosure of the amino acid sequence of SEQ ID NO:35 which is termed NAALAD-II in the this publication. See Figure 3 which also depicts the sequences of peptide regions constituting relative insertions and deletions of splicing variants of SEQ ID NO:35 set forth in SEQ IDs NOs: herein . Applicant's Amendment to the specification filed 2 July 2001 provides this information at page 1 of the specification.

Information Disclosure Statement

No Information Disclosure Statement [IDS] has yet been filed in this application but several documents supplied by Applicant and cited in the International Search Report in the parent International Application are made of record herewith on the accompanying form PTO-892.

Preliminary Amendment

Applicant's Preliminary Amendments filed 12 January 2001 and 12 March 2005 have been entered, providing a reference to related applications at page 1 of, and inserting Sequence Identifiers throughout, the specification as well as amending claims 9, 14, 17, 18, 20-30, 34, 35, 37, 43 and 44. Claims 1-48 remain in the application of which claims 10 and 11 are examined in accord with Applicant's Election made on 28 February 2006.

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Election

Applicant's election without traverse of the invention of Group 4, comprising claims 10 and 11, wherein the species of human NAALADase L protease having the amino acid sequence set forth in SEQ ID NO:35 is elected without traverse, in the reply filed on 28 February 2006 is acknowledged. Claims 10 and 11 are examined herein.

Specification

Applicant's submission of a Sequence Listing in both printed and computer readable forms, as well as a Statement Pursuant to 37 CFR § 1.821(f) and 37 CFR § 1.825(a) and (b), on 21 March 2005 in a *bona fide* attempt to comply with the requirements of 37 CFR § 1.821. Yet no part of the Sequence Listing filed 21 March 2005 describes, and no appropriate Sequence Identifier designates, any of the **integral** protease amino acid sequences of the splice variants apparently intended by the elected claim 11 which is construed to embrace the amino acid sequences of disclosed NAALADase-L variants that arise naturally due to differential splicing of a NAALADase-L-encoding mRNA transcript. Amending claim 11 to describe a variant only by the presence, or absence, of a peptide Sequence Identifier of SEQ IDs NOs:37-40, 42, 44 and 46 would be an inadequate description of such a variant protease.

Thus, compliance with 37 CFR § 1.821 is required in response to this Office action and a further Notice to Comply accompanies this communication. 37 CFR § 1.821 also requires that sequence identifiers accompany descriptions of defined nucleotide and amino acid sequences in the claims as well as in the specification with a designation properly stated as "**SEQ ID NO:n**" where "n" is an integer corresponding to the Sequence Disclosure. See 37 CFR §§ 1.821(b), (c) and (d). Yet claims 10 and 11 have no designations describing their subject matters according to the requirements of 37 CFR § 1.821 for a Sequence Disclosure. Even if an amino acid sequence were set

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forth in a claim, a recitation of a nucleotide or amino acid sequence positions must also include a statement of the designation, "**SEQ ID NO:n**". Applicant must revise both the printed and computer readable forms of the Sequence Disclosure to provide **integral** protease amino acid sequences for the NAALADase-L splice variants, with appropriate Sequence Identifiers, and submit a further Pursuant to 37 CFR § 1.821(f) and 37 CFR § 1.825(a) and (b) in response to this communication and must also amend claims 10 and 11 to include appropriate Sequence Identifiers for each NAALADase-L amino acid sequence that Applicant intends to claim.

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 10 and 11 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Claims 10 and 11 do not describe a "new . . . composition of matter" as required by the statute because they fail to distinguish a protease that is present in Nature in its native state from a protease that is a discovery, an invention reduced to practice by the efforts of a person. This rejection may be overcome by amending claim 10 to introduce an appropriate, distinguishing, term such as, e.g., "[a]n **isolated** protease".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10 and 11 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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The specification fails to exemplify or describe the preparation of the subject matters of the unspecified, divergent, proteases of claim 10 where the claim reaches generic proteases that differ to an indeterminate extent from the amino acid sequence of SEQ ID NO:10 but the specification describes only specific, particular, alterations that arise due to differential splicing of an encoding cellular RNA transcript rather than any modification by a person. Claim 11 is included in this rejection because, although it suggests a more limited set of protease species, it recites "or including the insertions or deletions . . . illustrated in Figure 3" the term "including" is construed as "comprising" thus the claim cannot limit the scope of claim 10 from which it depends. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification furnishes no relevant identifying characteristics of a protease that diverges to an indeterminate extent from the sequence of SEQ ID NO:35 and, when addressing the issue of whether a disclosure of a molecular structure of one polypeptide of one biological species could adequately describe the molecular structure of a functionally similar molecule of another biological species, the Court of Appeals for the Federal Circuit held that a claimed invention must be described with such "relevant identifying characteristic[s]" that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Because the specification provides only limited, specific, disclosures related to the subject matter of claim 10, the claimed subject matter is considered to be entirely prospective where skilled artisans in the relevant field of

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molecular biology could not predict the structure, or other properties, of the generic proteases of claim 10.

Claims 10 and 11 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the preparation of a protease having the amino acid sequence set forth in SEQ ID NO:35 and the preparation of splice variants of this protease having the specific peptide region insertions and deletions depicted in Figure 3 of the specification, does not reasonably provide enablement for the preparation of a generic protease having no particular structural relationship to SEQ ID NO:35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 10 contemplates an unlimited number of arbitrary assignments of any or all of amino acid substitutions, additions or deletions in the protease amino acid sequence set forth in SEQ ID NO:35, yet the specification does not support alterations of the amino acid sequence of SEQ ID NO:35 by amino acid insertions, deletions, or substitutions anywhere, in any combination or any pattern, in the protease amino acid sequence set forth in SEQ ID NO:35. Instead, the specification's Figure 3 discloses only particular insertions or deletions of specific peptide regions in the NAALADase-L protease amino acid sequence of SEQ ID NO:35. Claim 11 is included in this rejection because, although it suggests a more limited set of protease species, it recites "or including the insertions or deletions . . . illustrated in Figure 3" the term "including" is construed as "comprising" thus the claim cannot limit the scope of claim 10 from which it depends. Mere sequence perturbation cannot enable the design and preparation of a myriad, divergent, proteases and provide the public with a protease retains its native substrate specificity. This is demonstrated by the publication of Seffernick et al., 2001, **Journal of Bacteriology**, Vol. 183, No. 8, pages 2405-2410, made of record herewith, who teach that the alteration of 9 amino acids in a sequence of 475 amino acids, a scant 2% of the native amino acid positions, in a deaminase were sufficient to alter its substrate specificity and require it to catalyze different reactions even though, p. 2409, these

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alterations do not at all alter its tertiary structure and are spread throughout its primary structure.

It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (discussing factors relevant to an analysis of enablement). Applying the factors discussed in *Wands* to Applicant's disclosure, it is apparent that:

- a) the specification lacks adequate, specific, guidance for altering the sequence of SEQ ID NO:35 to the unspecified extent permitted by claim 10,
- b) the specification lacks working examples wherein SEQ ID NO:35 is altered to the unspecified extent permitted by claim 10,
- c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,
- d) unpredictability exists in the art where no members of the class of proteases represented by amino acid sequence of SEQ ID NO:35, have sustained an unspecified degree of amino acid modification and retained their native catalytic activity.

Thus the scope of subject matters embraced by claims 10 and 11 is unsupported by the present specification even if combined with teachings available in the prior art.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 and 11 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10 and 11 are both indefinite because they lack a basis for determining the structure of a starting NAALADase-L, i.e., they lack Sequence Identifiers of the form "SEQ ID NO:n" where n is an integer corresponding to an entry in the Sequence Listing that can provide the artisan and the public with a starting point to begin to measure the metes and bounds of the intended subject matter. Compliance with 37 CFR § 1.821 as

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detailed in the accompanying Notice to Comply will overcome this aspect of the rejection of claims 10 and 11.

Claim 10 is rejected as indefinite for its recitation, "or a functional equivalent or derivative thereof", because it fails to set forth the nature of the function an intended equivalent or derivative must retain. The artisan and the public seeking to ascertain the metes and bounds of the intended subject matter cannot determine what is part of, and what is excluded from, the claim. Claim 11 is included in this rejection because it fails to resolve the ambiguity of claim 10 from which it depends by indicating the nature of the "function" its equivalents or derivatives "include". Amending claim 10 to recite a specific, disclosed, function will overcome this aspect of the rejection of claims 10 and 11.

Claim 11 is separately rejected as indefinite because it recites, "including the insertions or deletions . . . illustrated in Figure 3", but fails to indicate how and where the "insertions or deletions" are to be included or what else is, or is not, to be "included" in a claimed protease. The artisan and the public seeking to ascertain the metes and bounds of the intended subject matter cannot determine what is part of, and what is excluded from, the claim. Amending claim 11 to state specific, integral, amino acid sequences of NAALADase-L splice variants, e.g., in the form of a Markush group, using the Sequence Identifiers provided in a revised Sequence Listing will overcome this rejection of claim 11.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The changes made to 35 U.S.C. § 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily

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published under 35 U.S.C. § 122(b). Therefore, this application is examined under 35 U.S.C. § 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).

Claim 10 is rejected under 35 U.S.C. § 102(a) as being anticipated by Shneider et al., made of record herewith, who anticipate the subject matter of claim 10 by disclosing in Figure 7 the amino acid sequence of an N-acetylaspartylglutamate peptidase sharing 81.4% identity with SEQ ID NO:35 herein, constituting a "functional equivalent" thereof.

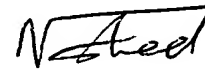
Claim 10 is rejected under 35 U.S.C. § 102(a) as being anticipated by Luthi-Carter et al., made of record herewith, who anticipate the subject matter of claim 10 by disclosing in Figure 3 the amino acid sequence of a rat NAALADase that shares 81.7% identity with SEQ ID NO:35 herein, constituting a "functional equivalent" thereof.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore
28 April 2006



NASHAAT T. NASHED PHD.
PRIMARY EXAMINER